Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.

SUPPLEMENTARY APPENDIX

COLLABORATORS

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Figure 1 – CONSORT Diagram

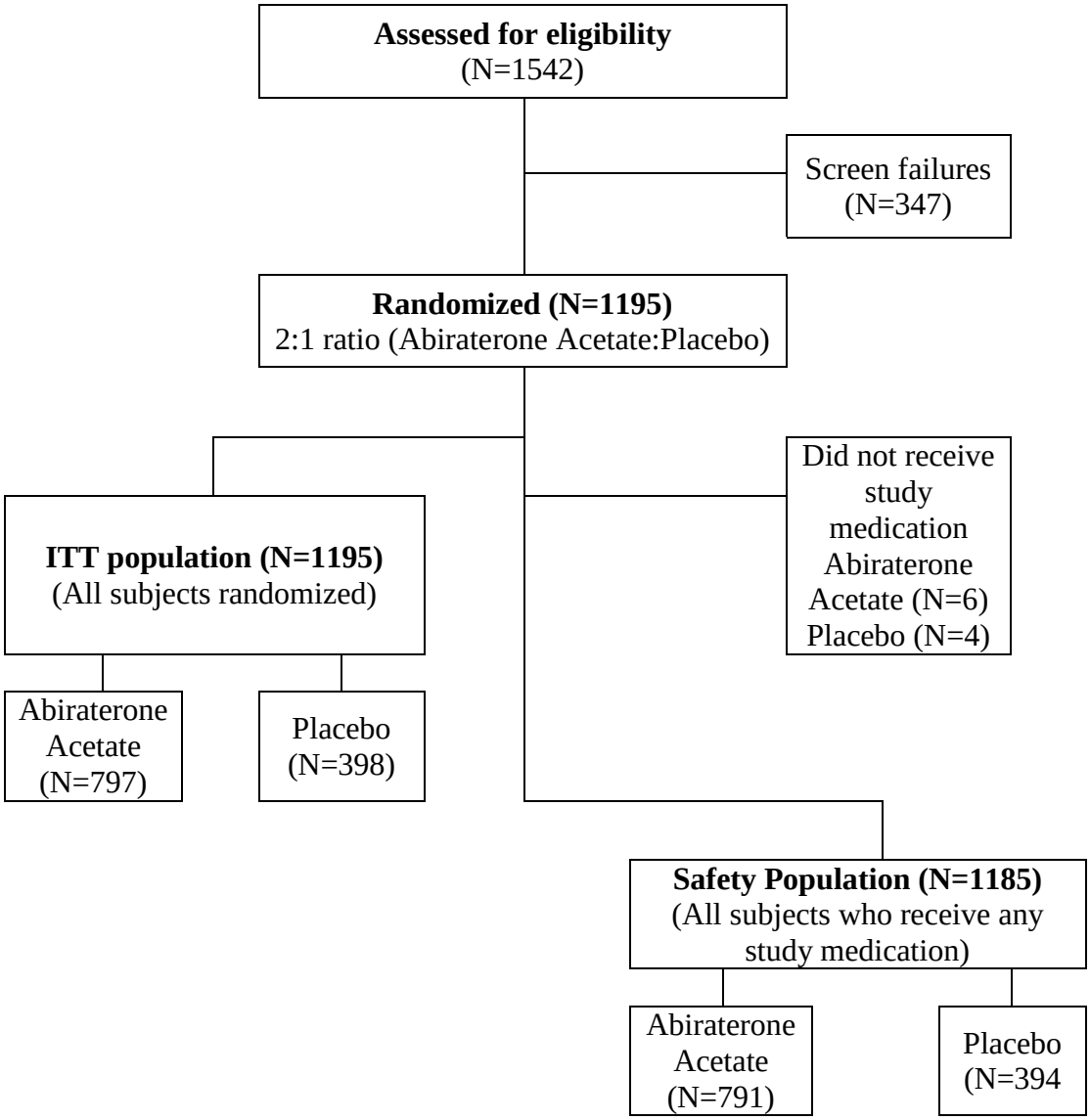

Table 1: Definition of End Points

Endpoint Variable	Definition
PSA response rate	PSA decline of ≥50% confirmed by a second PSA decline at least 4 weeks later.
PSA progression by pre-specified prostate cancer working group criteria	1) In patients whose PSA has not decreased, PSA progression is defined as a 25% increase over the baseline and an increase in the absolute-value PSA level by at least 5 ng/mL, which is confirmed by a second value, 2) In patients whose PSA has decreased but has not reached response criteria (PSA ≤50%), progressive disease would be considered to have occurred when PSA increases 25% over the nadir, provided that the increase is a minimum of 5 ng/mL and is confirmed, 3) If at least a 50% decline in PSA has been achieved, the PSA progression is an increase of 50% above the nadir at a minimum of 5 ng/mL.

Progression-free survival by prespecified radiographic criteria	Per investigator's assessment of progression by soft tissue (according to modified RECIST criteria [baseline lymph node ≥2.0 cm to be considered target lesion], or progression by bone scans with ≥2 new lesions not consistent with tumor flare.
Pain palliation rate	A reduction of ≥30% in the BPI-SF worst pain intensity score over the last 24 hrs observed at two consecutive evaluations 4 weeks apart without any increase in analgesic usage score. Only patients experiencing a pain score ≥4 at baseline were included.
Time to first skeletal-related event	A skeletal-related event was defined as pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

BPI-SF, brief pain inventory-short form, RECIST, Response Evaluation Criteria In Solid Tumors

Table 2: Demographics and Baseline Disease Characteristics

	Abiraterone Acetate (N=797)	Placebo (N=398)
Gleason score at initial diagnosis		
N	697	350
≤7	341 (48.9%)	161 (46.0%)
≥8	356 (51.1%)	189 (54.0%)
PSA at initial diagnosis (ng/mL)		
N	619	311
Median	27.00	35.50
Range	0.1-16065.9	1.1-7378.0
Previous cancer therapy		
N	797	398
Surgery	429 (54%)	193 (49%)
Radiotherapy	570 (72%)	285 (72%)
Hormonal	796 (100%)	396 (100%)
Other[a]	797 (100%)	398 (100%)
Extent of disease		
Viscera, not otherwise specified	1 (0.1%)	0 (0.0%)

Lungs	103 (13%)	45 (11%)
Prostate mass	60 (8%)	23 (6%)
Other viscera	46 (6%)	21 (5%)
Other tissue	40 (5%)	20 (5%)
Baseline hemoglobin (g/dL)		
N	779	389
Median	11.8	11.8
Range	7.3-16.1	7.2-16.5
Baseline LDH		
N	783	386
Median	223.0	237.5
Range	84-3373	123-5125

[a]Including chemotherapy; PSA, prostate-specific antigen, and LDH, lactate dehydrogenase

Table 3 Dose Modifications

	Abiraterone Acetate (N=791)	Placebo (N=394)
Total treatment duration (weeks)		
N	791	394
Median	32.14	15.50
Range	(0.7-80.7)	(0.6-82.3)
Total number of cycles started		
N	791	394
Median	8.0	4.0
Range	(1-21)	(1-21)
Number of abiraterone acetate dose reductions		
0	763 (96.5%)	389 (98.7%)
1	23 (2.9%)	5 (1.3%)
2	5 (0.6%)	0 (0.0%)
Reason for abiraterone acetate dose reduction*	28 (3.5%)	5 (1.3%)
Adverse event or toxicity	13 (1.6%)	1 (0.3%)

Serious adverse event or hospitalization	2 (0.3%)	0 (0.0%)
Restart dosing	13 (1.6%)	3 (0.8%)
Number of prednisone/prednisolone dose reductions		
0	765 (96.7%)	390 (99.0%)
1	26 (3.3%)	4 (1.0%)
>1	0	0
Reason for prednisone/prednisolone dose reduction*	25 (3.2%)	4 (1.0%)
Serious adverse event	1 (0.1%)	0
Toxicity or other adverse event	13 (1.6%)	1 (0.3%)
Re-start dosing	1 (0.1%)	1 (0.3%)
Other	11 (1.4%)	2 (0.5%)

*Patients having multiple dose modifications were counted only once on each line but may be represented on more than one line.

Minutes of Meeting of the Independent Data Monitoring Committee (IDMC) for the COU-AA-301 study – Teleconference, Aug 20th, 2010

Participants: Drs Ralph Harkins, Sten Nilsson, Ian Tannock (chair), Nick Thatcher **(**IDMC members), Mr Greg. Dozier (Novella)

The IDMC determined their response to the following questions posed by the sponsor representatives, Drs Peter Ho and Gordon Lan:

1. *Does the IDMC recommend that the study be continued with or without modification(s)? If so, what are the recommended modifications?*

   No

If "No" to Question (1), then:

2. *Has the interim analysis crossed the boundary for statistical significance for the primary endpoint of OS at the pre-specified two-sided p-value ≤ 0.01416? (Please note that we recalculated the p-value cut-off and hazard ratio based on the larger number of events at the interim analysis vs. that estimated in the protocol)*

   Yes.

3. *Has the interim analysis resulted in the expected magnitude of treatment effect size with an observed hazard ratio ≤ 0.811 for the primary endpoint of OS?*

   Yes

4a. Are there any data issues identified in the safety or efficacy (primary or secondary) results that the IDMC wishes to highlight or discuss?

   No major issues – see summary of safety review above.

4b. Is the IDMC concerned that any data issues may affect the robustness of the interim analysis results?

   No

5a. Does the IDMC consider the interim analysis results to be clinically significant for the patient population under study?

   Yes

5b. If the primary endpoint is considered clinically significant, considering the observed safety profile, does the IDMC consider the overall risk:benefit ratio to favor the experimental arm?

   Yes

5c. Based on the interim analysis, does the IDMC recommend that the study be halted and that patients in the control group be crossed over to the experimental treatment?

   Yes. Also the IDMC views it as highly unlikely that offering study drug to those patients on the placebo arm who are alive and fit to receive it will confound the survival analysis in a meaningful way

6. As this is a registration study, it will undergo a critical review by regulatory agencies whereby alternative analyses may result in the exclusion of patients from the intent-to-treat analysis, does the IDMC consider the observed results robust enough to allow for potential patient exclusions that may reduce the statistical significance of the results to date?

Yes, the observed results are very robust.

At the conclusion of the closed session the chair invited Drs Ho and Lan to rejoin the teleconference and communicated to them the above recommendations.
The IDMC members expressed their congratulations to the study team and reinforced that their deliberations and all data relating to the study remain confidential.

Ian Tannock MD, PhD, DSc
Chair of the IDMC &
Professor of Medicine, University of Toronto

Toronto,
Aug 25th, 2010